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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,809	02/02/2005	Koji Kawai	TIP-04-1339	9964

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,809	KAWAI ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Drawings of the compound of formula 1 .

DETAILED ACTION

The response filed **October 10, 2006** presents remarks and arguments to the office action mailed **July 07, 2006**. Applicants' request for reconsideration of the rejection of claims in the last office action has been considered.

Applicants' arguments, filed, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of claims

Claims 7-10 are cancelled.

Claims 11-22 are pending.

Claims 20-22 are newly added claims

Claim 13 and 21 are withdrawn by examiner as it is to a non-elected specie.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-16, 20 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating nausea and or vomiting,

does not reasonably provide enablement for preventing nausea or vomiting. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Nature of the invention.

The nature of the invention is directed to a method of preventing nausea caused by μ-opioid agonist compound by administering naltrindone compound of formula I. The term "prevention" encompasses the philosophy, credo, programs, and practices that aim to defer or eliminate diseases, disability, and other forms of human suffering from ever happening.

2) State of the prior art and the predictability or lack thereof in the art.

How can one prevent emesis, Applicant has not shown how prevention can take place. In the specification it is taught that the effect of emesis or vomiting is reduced. Administering to compound to the set population will vary per the patient response to that drug, since only a few percentage of the population does not permit the use of prevention. The state of the prior art is that it involves screening *in vivo* to determine which how the set population exhibits the desired pharmacological activities (i.e. no vomiting, vomiting after a set time, or the notion to vomit after the patient have received the toxic agent that causes vomiting. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Next understanding the mechanism of chemotherapy induced emesis is complex and depends on various neurotransmitters and neurotransmitter receptors. If a wide variation of this is still on known how can prevention take place?

Thus, in the absence of a showing of how prevention is carried out by administering the compounds of the instant claims, one of skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of the different agents administered to the patient.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. The compound of the claimed invention would need testing with a wide variation of toxic agents that cause vomiting upon administration.

4) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is found on pages 27-28 wherein different compounds was used to identify and evaluate the anti-emetic effect. However, that only showed reduction and not prevention

5) Existence of working examples.

As discussed above, working example is found on pages 27-28 Applicant's. Prevention was not shown, only reduction. Limited working example does not enable one of skill in the art to treat the numerous toxic agents with the claimed amounts of diseases encompassed by the instant invention for the use of the term prevention.

Response to Arguments

Applicant's arguments, filed, with respect to the rejection(s) of claim(s) 11-12 and 14-19 under 103(a) have been fully considered and are unpersuasive. The specie election is withdrawn, the rejection is applied to include the non-elected species of the claim invention, and that includes naltraxone, and naloxone.

Applicant argues that the Portoghese et al. did not specifically teach treating vomiting but only the notion of treating selected side effects (see page 6).

Next Applicant argues the teaching only indicates generality that the opioid ligand itself which bonds to one type for example μ can be those having no side effects.

Also Applicant argues that Rudd did not disclose naltrindole but rather naltraxone and naloxone.

In response, the Portoghese et al. (see col. 1, background section, lines 19-30) teaches the various side effects of morphine dependence, vomiting is one of them and the drug used in the said reference is naltrindone. One of ordinary skill in the art would

expect the properties of the chemical to be same if the same drug is administered. Also morphine is highly toxic, one such limitation of the instant claim 17. Thus the reference is appropriately applied to the said teachings.

Secondly, with regards to the Rudd et al reference, the argument is unpersuasive because the effect is to reduce emesis in patients, wherein the emesis is caused by a particular toxic agent, a toxin, clearly the emesis is caused by the administering of the drug.

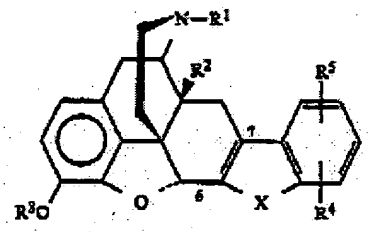
New Claim Rejections - 35 USC § 103

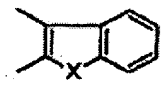
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Portoghese et al. US 5, 352,680 (of record) taken with of Rudd et al. Europ. J. Pharm. (of record) in view of Choi et al. Can. J. Anaesth. 47(1) (2000) 33-37.

Portoghese et al. teach a compound that is structurally identical to that of the claimed compound as  (see col. 14, lines 10 +) as in claims 11 and 12, where R^1 is an alkyl group having 1-5 carbon atoms, R^{2-4} are hydrogen, or R^4 and R^5 together form an O, (as in claim 14) R^6 is hydrogen and Q is



(see col. 14 lines 10-30).

With regards to claim 15, the above reference teaches, if a ligand acts at a single opioid receptor type or subtype, the potential side effects mediated through other opioid receptor types can potentially be minimized or eliminated, thus treating or preventing nausea and vomiting (see col. 1, lines 34-43) and the μ-opiod agonist compound is a morphine (see col. 9 lines 8-17).

As to claim 17 and 19, the nausea or vomiting is caused by gastrointestinal dysfunction (characterized as smooth muscles of the gastrointestinal, biliary, and urinary tracts causing constipation, gallbladder spasm, and urinary retention) (see col. 1, lines 20-23). Thus teaching gastrointestinal dysfunction.

Rudd et al. teach naltrindole, naltrexone and naloxone (drugs having the same core structure of that of naltrindone (see enclosed attached structures) to inhibit the emetic reflex (vomiting) (see abstract and also page 82 (section 4.3 first para.) as in claims 20-22. Also note that the anti-emetic action of fentany is antagonized by the opioid receptor antagonist naltrxone.

Choi et al. teach naloxone reduces nausea in a post operative epidural pain (see page 34 highlighted sec.).

Portoghese et al. teach the compound is an opiod antagonist and belongs to a group of morphinan derivatives.

One of ordinary skill in the art would have been motivated to administer the above compounds to a patient wherein the nausea and vomiting is caused by radiation, toxic agent post operative and or gastrointestinal dysfunction because the art teaches that drugs with the same core structure varying in only substitution of the compound of formula I would have resulted in reducing emesis. The motivation comes from Rudd et al., where it teaches the comparative effect of the various drugs on fentanyl. Therefore one of ordinary skill in the art would have been motivated to administer the drug since the compound as taught has the property of reducing vomiting/nausea as a whole, and would expect the drug to work since the action of is blocking of the stimulation of the emesis zone as it was found to be a member of the morphinan that prevents emetics. It would therefore have been prima facie obvious to the skilled artisan at the time the invention was made to administer the drug for the treatment of nausea or vomiting as indicated by the above cited prior art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
6/20/06

Ardin H. Marschel 1/6/07
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